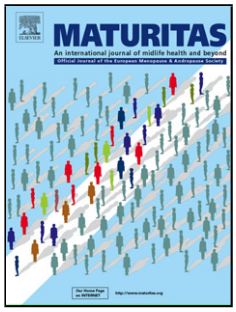

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PII: S0378-5122(16)30342-5
DOI: http://dx.doi.org/doi:10.1016/j.maturitas.2016.11.006
Reference: MAT 6724

To appear in: *Maturitas*

Received date: 21-3-2016
Revised date: 8-10-2016
Accepted date: 11-11-2016

Please cite this article as: Bano Giulia, Trevisan Caterina, Carraro Sara, Solmi Marco, Luchini Claudio, Stubbs Brendon, Manzato Enzo, Sergi Giuseppe, Veronese Nicola.Inflammation and sarcopenia: A systematic review and meta-analysis.*Maturitas* http://dx.doi.org/10.1016/j.maturitas.2016.11.006

INFLAMMATION AND SARCOPENIA:

A SYSTEMATIC REVIEW AND META-ANALYSIS

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Highlights

- Sarcopenia is associated with functional impairment and adverse outcomes.
- Highly inflammatory cytokines are negatively related to muscle strength and mass.
- Sarcopenia is associated with higher serum inflammatory parameters.
- Chronic inflammation could play a role in sarcopenia.

Abstract

Inflammatory cytokines have been shown to prompt muscle wasting, ultimately stimulating protein catabolism and suppressing muscle synthesis. However, the possible association between inflammatory parameters and sarcopenia is poorly understood. We therefore aimed to summarize the current evidence about this topic with a meta-analysis of studies reporting serum inflammatory parameters in patients with sarcopenia vs. people without sarcopenia (controls). An electronic PubMed and Scopus search through to 09/01/2016 and meta-analysis of cross-sectional studies comparing serum levels of inflammatory cytokines between patients with sarcopenia and controls was made, calculating random-effects standardized mean differences (SMDs) ±95% confidence intervals (CIs) as the effect size. Out of 1370 initial hits, 17 studies with a total of 11249 participants (3072 with sarcopenia and 8177 without) were meta-analysed. Sarcopenic participants had significantly higher levels of CRP (SMD=0.51; 95%CI 0.26, 0.77; $p<0.0001$; $I^2=96\%$) than controls. Conversely, serum IL6 levels were not significantly different (SMD=0.35; 95%CI: -0.19, 0.89; $p=0.21$; $I^2=97\%$) in people with sarcopenia versus controls. Sarcopenic people did not have higher levels of TNF-α than controls (SMD=0.28; 95%CI -0.26, 0.83; $p=0.31$; $I^2=97\%$). In conclusion, sarcopenia seems to be associated with elevated serum CRP levels; future longitudinal studies are needed to clarify this relationship.

Keywords: sarcopenia; inflammation; meta-analysis; C reactive protein.

1. Introduction

Inflammation is an adaptive response of the immune system triggered by a homeostatic imbalance, to restore functionality. Whereas the acute inflammatory process induced by infection or tissue injury is clear, considerably less is known about the deleterious effects of chronic low-grade inflammation. The oxidative stress-induced redox imbalance and the sustained upregulation of pro inflammatory mediators are believed to act as the patho-physiological basis underpinning inflammatory disorders including cardiovascular diseases, cancer, diabetes, dementia and also sarcopenia [1].

According to the recent definitions of several working groups, sarcopenia is described as a syndrome characterized by a loss of muscle mass and strength with functional impairment and adverse outcomes [2], [3]. The age related muscle loss coincides with a micro and macro architecture disorganization of the entire muscle mass. For instance, the conversion of type II (fast) fibers to type I (slow) fibers and subsequent lipid infiltration, which translate into impairment of muscle power and a greatly increased risk of falls [4]. Several studies have shown that sarcopenic individuals are either three times more likely to fall or have an higher risk of death relative to non sarcopenic individuals [5], [6]. Moreover, sarcopenia itself is associated with disability and hospitalization [7].

A substantial body of literature has demonstrated that inflammatory cytokines activate many of the molecular pathways involved in skeletal muscle wasting leading to an imbalance between protein synthesis and catabolism [8], [9]. High levels of inflammatory cytokines have been demonstrated to be negatively related to muscle strength and mass [10], [11]. However, the research considering whether their serum cytokine levels could represent a biological marker of sarcopenia is equivocal [12].

Therefore, we conducted a systematic review and meta-analysis of observational studies exploring the association between serum inflammatory parameters and sarcopenia. We hypothesized that participants with sarcopenia have higher inflammatory parameters levels than normal controls.

2. Methods

This systematic review was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for the quality assessment of included studies [13] and the indications of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. [14]

2.1 Search Strategy

Two investigators (MS, CL) independently conducted an electronic literature search using PubMed and Scopus, without language restriction, from database inception until 09/01/2016. In PubMed, controlled vocabulary terms and the following keywords were used: ("sarcopenia"[All Fields]) AND (("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) OR inflammatory[All Fields] OR IFN[All Fields] OR ("interferons"[MeSH Terms] OR "interferons"[All Fields] OR "interferon"[All Fields]) OR TNF[All Fields] OR "tumor necrosis factor"[All Fields] OR IL[All Fields] OR "interleukin"[All Fields] OR "TGF"[All Fields] OR ("apoptosis"[MeSH Terms] OR "apoptosis"[All Fields]) OR apoptotic[All Fields] OR antiapoptotic[All Fields] OR CRP[All Fields] OR "C-reactive protein"[All fields] OR ("cytokines"[MeSH Terms] OR "cytokines"[All Fields] OR "cytokine"[All Fields])). A similar search strategy was run in Scopus. Conference abstracts were also considered and at least 4 attempts were made to contact study authors for additional information. Reference lists of included articles and those relevant to the topic were hand-searched for identification of additional, potentially relevant articles.

2.2 Study Selection

Included were studies that (1) compared data on inflammatory parameters between participants with sarcopenia vs. those without, (2) reported on serum levels of inflammatory cytokines, and (3)

reported data about muscular mass assessed with Dual-energy X-ray Absorptiometry (DXA) , Magnetic Resonance Imaging (MRI) or bioimpendenziometry (BIA) and not only with body composition estimates (e.g. calf circumference). Studies were excluded if they (1) did not use clear diagnostic criteria for sarcopenia, (2) measured only in vitro parameters or used animal models, or (3) did not measure or did not report quantitative cytokine levels in both sarcopenic and no sarcopenic subjects.

We also contacted authors asking for further information when: 1) data could not be meta-analyzed (i.e., no mean and standard deviation (SD) or equivalent for inflammatory parameters), 2) other relevant information was missing, 3) data about muscular mass were reported, but sarcopenia diagnosis no. At least 4 attempts were made with these Authors.

Study data consisting of cytokine levels with SDs larger than three times the mean were excluded from the analyses, as we considered these to be overly skewed and unreliable. [15]

2.3 Data Extraction

Two authors (CT, SC) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information were extracted: i) study population characteristics (e.g., sample size, demographics); ii) clinical setting in which the study was performed; iii) parameters related to sarcopenia and inflammation (age, gender, body mass index) in sarcopenic and no sarcopenic subjects, iv) diagnostic criteria for sarcopenia, and v) method of evaluation of inflammatory cytokines.

2.4 Assessment of study quality

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria [13] were used for the quality assessment of included studies. One Author made the assessment of

quality (MS) and any discrepancies were addressed by a joint re-evaluation of the article with other two investigators (NV and EM).

2.5 Statistical Analysis

The meta-analysis was performed using Review Manager (RevMan) Version 5.3 for Windows (Cochrane Collaboration, http://ims.cochrane.org/revman). Only outcomes with at least two studies were meta-analyzed, while outcomes with only one study were reported in the descriptive analyses. When combining studies, the random effects model was used to account for study heterogeneity [16] using standardized mean difference (SMD) with its 95% confidence interval (CI).

Study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p \leq 0.05$ and I-squared $\geq 50\%$ indicating the presence of significant heterogeneity. [16] For significant outcomes including ≥ 4 studies and with significant heterogeneity, we conducted a meta-regression analysis to explore if some variables of the characteristics of the all sample/study or differences in some characteristics between those having sarcopenia and those without were significant moderators. Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau [17] and Egger bias test [18] for outcomes having at least 4 studies. Meta-regression and publication bias analyses were conducted using Comprehensive Meta-Analysis V3 (http://www.meta-analysis.com/index.php).

3. Results

The search identified 1370 potentially eligible studies, of which 354 duplicates were excluded due to duplication. After excluding 978 papers through title and abstract review, 38 full text articles were examined. Altogether, 19 studies were included in the qualitative synthesis [11], [19]–[36] and 17 in meta-analysis [20]–[36] (**eFigure 1**).

3.1 Study and Patient Characteristics

Studies and patients characteristics are summarized in **eTable 1**. The 17 meta-analyzed studies

[20]–[36] included a total of 11249 participants (3072 with sarcopenia and 8177 without). The majority of the studies were conducted in Asia and among outpatients (**eTable 1**). All of the studies were published in the last five years.

Sarcopenic subjects had a mean age of 66.3±6.9 years, a mean BMI of 20.7±3.4 and were slightly higher proportion of men (51.5%). People without sarcopenia were a mean age of 66.2±6.5 years, had a mean BMI of 25.4±2.7 and just over half of the proportion were men (51%) (**eTable 1**).

STROBE quality indicators (**eTable 2**) indicated that only poor information about clearly defined exposure ascertainment could be a potential source of bias being present in two studies among seventeen [20], [33] included in our meta-analysis. However, for these studies we obtained additional data from the Authors, hence detail was not addressed in the primary paper.

3.2 Cross-sectional studies reporting on serum CRP, IL6 and TNF-α levels

Pooling data from 16 studies [20]–[33], [35], [36], people with sarcopenia (n=3391) were significantly more likely than those without sarcopenia (n=7658) to have significantly higher levels of CRP (SMD=0.51; 95%CI: 0.26, 0.77; p<0.0001; I^2=96%) (**Figure 1**). On the contrary, serum IL6 levels did not differ between people with sarcopenia (n=1113) versus those with sarcopenia (n=1981) (7 studies [22], [26], [29], [30], [33]–[35]; SMD=0.35; 95%CI: -0.19, 0.89; p=0.21; I^2=97%) (**Figure 2**). Similarly, people with sarcopenia (n=1031) had similar levels of TNF-α compared to those without sarcopenia (n=1767) (5 studies [22], [26], [29], [33], [35] ; SMD=0.28; 95%CI: -0.26, 0.83; p=0.31; I^2=97%) (**Figure 3**).

3.3 Meta-regression analysis

Since the analysis investigating CRP as outcome was significant, but had a high heterogeneity (I^2=96%, p<0.0001), we conducted meta-regression analyses in order to detect potential moderators of this heterogeneity. As reported in **eTable 3,** only the country in which the study was conducted (β=0.64; 95%CI 0.24, 1.03 p=0.0016; R^2=0.54) and the differences in the percentage of females

between people with and without sarcopenia (β=-0.04; 95%CI 0.02, 0.05, p<0.0001; R^2=0.76, **eFigure 3**) emerged as potential moderators of the heterogeneity.

After stratifying for country (Europe+America vs. Asia), median of sample size (=177) and setting (community-dwelling vs. other settings), however, CRP remained significantly higher in those with sarcopenia vs. those without although SMD resulted larger in studies made in Asia and in studies with more than 177 participants (**eTable 4**).

3.4 Publication Bias

As seen in funnel plots (**eFigure 3**) and confirmed by the Begg's (tau=0.68, p=0.46) and Egger's test (intercept=5.84±2.54, p=0.31), no publication bias was evident for CRP, no publication bias emerged for both IL6 (tau=0.84, p=0.74; Egger's=1.28±0.84, p=0.24) or TNF-α (tau=0.21, p=0.14; Egger's=2.74±1.54, p=0.44) .

3.5 Descriptive findings

One study [19] reported a no significant difference in monocyte chemoattractant protein-1 (MCP-1) between sarcopenic and no sarcopenic subjects, whereas in a prospective, population-based study suggest higher levels of IL-6 and CRP increase the risk of muscle strength loss in older men and women [11].

4. Discussion

In this meta-analysis, involving 3072 people with sarcopenia and 8177 controls, we found evidence suggesting a significantly elevated inflammatory marker profile in people with sarcopenia. To the best of our knowledge, this is the first meta-analysis to investigate the possible relationship between sarcopenia and inflammation. Specifically, patients with sarcopenia experienced significantly higher levels of CRP, whilst no significant differences emerged for IL6 and TNF-α compared to controls. Although the analysis investigating CRP as outcome was characterized by a high heterogeneity, we

explained the majority of this with our meta regression analyses.

Surprisingly, sarcopenia was associated with higher serum CRP levels, but not with higher IL6 or TNF-α compared to the controls. These findings are in agreement with our recent work regarding the relationship between frailty and inflammation [37] showing that CRP is more strictly related to frailty than IL6 and TNF-α. Whilst the exact reason for this difference is not clear, it might by hypothesized that the number of studies and participants (more limited for IL6 and TNF-α) could play a role in these findings. Although our findings should be clarified and further explored with future longitudinal studies, our results support the notion that CRP could be a potential parameter for detecting sarcopenia.

Contrary to our findings, a previous narrative review [12] distinguished sarcopenia and cachexia, which is defined as a multifactorial syndrome accompanied by anorexia and loss of muscle mass not fully reversed by nutritional support [38]. The authors, hypothesed that sarcopenia may result from other mechanisms such as age related decline in hormones, neurodegenerative processes and disability, but not necessarily from inflammation [12]. Nevertheless, according with a different and emerging research and consistent with our results, sarcopenia may be associated and even caused by inflammation albeit of a lesser degree compared to cachexia. Thus, the inflammatory response driven by the underlying disease is thought to be very prominent in cachexia whilst seems to be lower and chronic in sarcopenia, but finally leading, in both syndromes, to muscle proteolysis and myocyte apoptosis [39], [40]. The positive association between sarcopenia and inflammatory parameters is also in agreement with a study from Visser et al. who demonstrated that inflammatory parameters were inversely related to handgrip strength [10]. Our findings may suggest that the plasma titre of some inflammatory molecules could be related to the aspects of muscle decline and function impairment; whether this association could be clinically relevant is controversial since the

phenotypical and pathophysiological complexity of sarcopenia could not be captured by single biological biomarkers but probably need a multidimensional approach [41].

Moreover, our meta-regression analysis suggests an important role of female gender in explaining the association between inflammation and sarcopenia. This finding seems to be pertinent with the current literature suggesting that female gender is characterized by higher inflammatory levels than men. [42]

There is growing interest in effective therapies to counteract the catabolic effect of chronic inflammation even if it is still limited to animal and in vitro models. Rieu and colleagues showed that the development of low grade inflammation may be controlled by an NSAID and the muscle protein synthesis restored in the postprandial state in old rats [43]. After 5 months, cytokines levels were significantly improved and muscle wasting significantly decreased in rats supplemented with ibuprofen compared to controls. The authors suggested that even a mild increase in cytokines production make the signalling pathways insensitive to food intake [43]. Moreover, NSAIDs appear to have a protective effect against muscle breakdown also in elderly people [44], but there are no sufficient data yet and further investigations may be warranted.

Whilst the current meta-analysis is a first, the findings should be considered along with its limitations. The most important of these lies in that the diagnosis of sarcopenia is mainly based only on muscular mass parameters, while current guidelines suggest that for this condition both physical performance and muscular mass should be decreased for a correct diagnosis of sarcopenia. Therefore, we were not able to investigate the association between physical function and inflammation. Second, the evidence relies substantially on data from cross-sectional studies, thus precluding any suggestion of causation. We included only one study in our meta-analysis dealing with the loss of handgrip strength and not with sarcopenia. Thus, future longitudinal research should seek to disentangle the directionality of the sarcopenia and inflammation. Another limitation is the high heterogeneity found in almost all the outcomes included. Although we were able to partially

explain the heterogeneity affecting the differences in CRP levels between sarcopenic and control subjects, other factors are probably important. Finally, we did not assess any intracellular markers of inflammation that could be highly related to serum parameters.

In conclusion, our meta-analysis found evidence that sarcopenia is associated with higher serum inflammatory parameters and in particular increased CRP levels. Future longitudinal research is required to disentangle and better understand the relationships we observed.

Contributors:

GB was responsible for producing the initial draft of the manuscript.
CT was responsible for data extraction and for producing the initial draft of the manuscript.
SC was responsible for data extraction.
MS was responsible for screening the papers and quality assessment.
CL was responsible for screening the papers.
BS was responsible for statistical analysis.
EM was responsible for quality assessment and revision of the manuscript.
GS was responsible for producing the initial draft of the manuscript.
NV was responsible for quality assessment, statistical analysis and revision of the manuscript.
All the authors approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for this review.

Provenance and peer review

This article has undergone peer review.

REFERENCES

[1] H. Y. Chung, M. Cesari, S. Anton, E. Marzetti, S. Giovannini, A. Y. Seo, C. Carter, B. P. Yu, and C. Leeuwenburgh, "Molecular inflammation: Underpinnings of aging and age-related diseases," *Ageing Res. Rev.*, vol. 8, no. 1, pp. 18–30, 2009.

[2] a J. Cruz-Jentoft, J. P. Baeyens, J. M. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. C. Martin, J. P. Michel, Y. Rolland, S. M. Schneider, E. Topinkova, M. Vandewoude, M. Zamboni, and P. European Working Group on Sarcopenia in Older, "Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People," *Age Ageing*, vol. 39, no. 4, pp. 412–423, 2010.

[3] J. E. Morley, A. M. Abbatecola, J. M. Argiles, V. Baracos, J. Bauer, S. Bhasin, T. Cederholm, A. J. Stewart Coats, S. R. Cummings, W. J. Evans, K. Fearon, L. Ferrucci, R. a. Fielding, J. M. Guralnik, T. B. Harris, A. Inui, K. Kalantar-Zadeh, B.-A. Kirwan, G. Mantovani, M. Muscaritoli, A. B. Newman, F. Rossi-Fanelli, G. M. C. Rosano, R. Roubenoff, M. Schambelan, G. H. Sokol, T. W. Storer, B. Vellas, S. von Haehling, S.-S. Yeh, and S. D. Anker, "Sarcopenia With Limited Mobility: An International Consensus," *J. Am. Med. Dir. Assoc.*, vol. 12, no. 6, pp. 403–409, 2011.

[4] T. Lang, T. Streeper, P. Cawthon, K. Baldwin, D. R. Taaffe, and T. B. Harris, "Sarcopenia: etiology, clinical consequences, intervention, and assessment.," *Osteoporos. Int.*, vol. 21, no. 4, pp. 543–559, 2010.

[5] F. Landi, R. Liperoti, A. Russo, S. Giovannini, M. Tosato, E. Capoluongo, R. Bernabei, and

G. Onder, “Sarcopenia as a risk factor for falls in elderly individuals: Results from the ilSIRENTE study,” *Clin. Nutr.*, vol. 31, no. 5, pp. 652–658, 2012.

[6] F. Landi, A. J. Cruz-Jentoft, R. Liperoti, A. Russo, S. Giovannini, M. Tosato, E. Capoluongo, R. Bernabei, and G. Onder, “Sarcopenia and mortality risk in frail olderpersons aged 80 years and older: Results from iLSIRENTE study,” *Age Ageing*, vol. 42, no. 2, pp. 203–209, 2013.

[7] L. Bianchi, L. Ferrucci, A. Cherubini, M. Maggio, S. Bandinelli, E. Savino, G. Brombo, G. Zuliani, J. M. Guralnik, F. Landi, and S. Volpato, “The Predictive Value of the EWGSOP Definition of Sarcopenia: Results From the InCHIANTI Study,” *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.*, no. January 2016, p. glv129, 2015.

[8] E. Jo, S.-R. Lee, B.-S. Park, and J.-S. Kim, “Potential mechanisms underlying the role of chronic inflammation in age-related muscle wasting.,” *Aging Clin. Exp. Res.*, vol. 24, no. 5, pp. 412–22, 2012.

[9] S. L. Budui and A. P. Rossi, “The pathogenetic bases of sarcopenia,” vol. 12, no. 2, pp. 22–26, 2015.

[10] M. Visser, M. Pahor, D. R. Taaffe, B. H. Goodpaster, E. M. Simonsick, A. B. Newman, M. Nevitt, and T. B. Harris, “Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study.,” *J. Gerontol. Med. Sci.*, vol. 57A, no. 5, pp. M326–M332, 2002.

[11] L. a. Schaap, S. M. F. Pluijm, D. J. H. Deeg, and M. Visser, “Inflammatory Markers and Loss of Muscle Mass (Sarcopenia) and Strength,” *Am. J. Med.*, vol. 119, no. 6, pp. 526.e9–526.e17, 2006.

[12] D. R. Thomas, “Loss of skeletal muscle mass in aging: Examining the relationship of starvation, sarcopenia and cachexia,” *Clin. Nutr.*, vol. 26, no. 4, pp. 389–399, 2007.

[13] E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche, J. P. Vandenbroucke, and for the STROBE initiative, “The Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement: guildelines for reporting observational studies," *J. Clin. Epidemiol.*, vol. 61, no. 4, pp. 344–349, 2008.

[14] A. Liberati, D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, J. P. A. Ioannidis, M. Clarke, P. J. Devereaux, J. Kleijnen, and D. Moher, "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.," *PLoS Med.*, vol. 6, no. 7, p. e1000100, 2009.

[15] M. Solmi, N. Veronese, A. Favaro, P. Santonastaso, E. Manzato, G. Sergi, and C. U. Correll, "Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies.," *Psychoneuroendocrinology*, vol. 51, pp. 237–52, Jan. 2015.

[16] J. P. T. Higgins and S. G. Thompson, "Quantifying heterogeneity in a meta-analysis," *Stat. Med.*, vol. 21, no. 11, pp. 1539–1558, 2002.

[17] C. B. Begg and M. Mazumdar, "Operating characteristics of a rank correlation test for publication bias.," *Biometrics*, vol. 50, no. 4, pp. 1088–1101, 1994.

[18] S. Duval and R. Tweedie, "Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis.," *Biometrics*, vol. 56, pp. 455–463, 2000.

[19] J. P. Lim, B. P. Leung, Y. Y. Ding, L. Tay, N. H. Ismail, A. Yeo, S. Yew, and M. S. Chong, "Monocyte chemoattractant protein-1: A proinflammatory cytokine elevated in sarcopenic obesity," *Clin. Interv. Aging*, vol. 10, pp. 605–609, 2015.

[20] J. L. Atkins, P. H. Whincup, R. W. Morris, and S. G. Wannamethee, "Low muscle mass in older men: The role of lifestyle, diet and cardiovascular risk factors," *J. Nutr. Heal. Aging*, vol. 18, no. 1, pp. 26–33, 2014.

[21] B. Can, B. Ozgur Kara, B. Muhammet Cemal Kizilarslanoglu, B. Gunes Arik, G. Sengul Aycicek, B. Fatih Sumer, and Z. Ulger, "Serum markers of inflammation and oxidative stress in sarcopenia," *Aging Clin. Exp. Res.*

[22] M. T. Dutra, B. Pereira Avelar, V. C. Souza, M. Bottaro, R. Jac O Oliveira, O. Avio, T. N. Obrega, R. Moreno Lima, and R. M. Lima, "Relationship between sarcopenic obesity-related

phenotypes and inflammatory markers in postmenopausal women Summary Correspondence."

[23] A. El Maghraoui, F. B. Ebo'o, S. Sadni, A. Majjad, T. Hamza, and A. Mounach, "Is there a relation between pre-sarcopenia, sarcopenia, cachexia and osteoporosis in patients with ankylosing spondylitis?," *BMC Musculoskelet. Disord.*, 2016.

[24] H. Fujikawa, T. Araki, Y. Okita, S. Kondo, M. Kawamura, J. Hiro, Y. Toiyama, M. Kobayashi, K. Tanaka, Y. Inoue, Y. Mohri, K. Uchida, and M. Kusunoki, "Impact of sarcopenia on surgical site infection after restorative proctocolectomy for ulcerative colitis," *Surg. Today*.

[25] H. Ishihara, T. Kondo, K. Omae, T. Takagi, J. Iizuka, H. Kobayashi, and K. Tanabe, "Sarcopenia and the Modified Glasgow Prognostic Score are Significant Predictors of Survival Among Patients with Metastatic Renal Cell Carcinoma Who are Receiving First-Line Sunitinib Treatment."

[26] P. Joppa, R. Tkacova, F. M. Franssen, C. Hanson, S. I. Rennard, E. K. Silverman, M.-L. N. McDonald, P. M. Calverley, R. Tal-Singer, M. A. Spruit, K. Kenn, E. F. Wouters, and E. P. Rutten, "Sarcopenic Obesity, Functional Outcomes, and Systemic Inflammation in Patients With Chronic Obstructive Pulmonary Disease."

[27] E. Y. Kim, Y. S. Kim, J.-Y. Seo, I. Park, H. K. Ahn, Y. M. Jeong, J. H. Kim, and N. Kim, "The Relationship between Sarcopenia and Systemic Inflammatory Response for Cancer Cachexia in Small Cell Lung Cancer."

[28] T. N. Kim, J. C. Won, Y. J. Kim, E. J. Lee, M. K. Kim, M. S. Park, S. K. Lee, J. M. Kim, K. S. Ko, and B. D. Rhee, "Serum adipocyte fatty acid-binding protein levels are independently associated with sarcopenic obesity," *Diabetes Res. Clin. Pract.*, vol. 101, no. 2, pp. 210–217, 2013.

[29] T. N. Kim, M. S. Park, K. Il Lim, H. Y. Choi, S. J. Yang, H. J. Yoo, H. J. Kang, W. Song, H. Choi, S. H. Baik, D. S. Choi, and K. M. Choi, "Relationships between sarcopenic obesity and

insulin resistance, inflammation, and vitamin D status: The Korean Sarcopenic Obesity Study," *Clin. Endocrinol. (Oxf).*, vol. 78, no. 4, pp. 525–532, 2013.

[30] J.-K. Kim, S. R. Choi, M. J. Choi, S. G. Kim, Y. K. Lee, J. W. Noh, H. J. Kim, and Y. R. Song, "Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease.," *Clin. Nutr.*, vol. 33, no. 1, pp. 64–8, 2014.

[31] M. E. Levine and E. M. Crimmins, "The Impact of Insulin Resistance and Inflammation on the Association Between Sarcopenic Obesity and Physical Functioning," *Obesity*, vol. 20, no. 10, pp. 2101–2106, 2012.

[32] K. E. Rollins, N. Tewari, A. Ackner, A. Awwad, S. Madhusudan, I. A. Macdonald, K. C. H. Fearon, and D. N. Lobo, "The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma," 2016.

[33] G. Sergi, S. Sarti, M. Mosele, E. Ruggiero, A. Imoscopi, F. Miotto, F. Bolzetta, E. M. Inelmen, E. Manzato, and A. Coin, "Changes in healthy elderly women's physical performance: A 3-year follow-up," *Exp. Gerontol.*, vol. 46, no. 11, pp. 929–933, 2011.

[34] L. Tay, Y. Y. Ding, B. P. Leung, N. H. Ismail, A. Yeo, S. Yew, K. S. Tay, C. H. Tan, and M. S. Chong, "Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults," *Age (Omaha).*, 2015.

[35] C. W. Yang, C. I. Li, T. C. Li, C. S. Liu, C. H. Lin, W. Y. Lin, and C. C. Lin, "Association of sarcopenic obesity with higher serum high-sensitivity c-reactive protein levels in Chinese older males - A community-based study (Taichung Community Health Study-Elderly, TCHS-E)," *PLoS One*, 2015.

[36] C. Van De Bool, E. P. A. Rutten, F. M. E. Franssen, E. F. M. Wouters, and A. M. W. J. Schols, "Antagonistic implications of sarcopenia and abdominal obesity on physical performance in COPD," *Eur. Respir. J.*, 2015.

[37] P. Soysal, B. Stubbs, P. Lucato, C. Luchini, M. Solmi, R. Peluso, G. Sergi, A. T. Isik, E. Manzato, S. Maggi, M. Maggio, A. M. Prina, T. D. Cosco, Y.-T. Wu, and N. Veronese,

"Inflammation And Frailty In The Elderly: A Systematic Review And Meta-analysis," *Ageing Res. Rev.*, 2016.

[38] K. Fearon, F. Strasser, S. D. Anker, I. Bosaeus, E. Bruera, R. L. Fainsinger, A. Jatoi, C. Loprinzi, N. MacDonald, G. Mantovani, M. Davis, M. Muscaritoli, F. Ottery, L. Radbruch, P. Ravasco, D. Walsh, A. Wilcock, S. Kaasa, and V. E. Baracos, "Definition and classification of cancer cachexia: An international consensus," *The Lancet Oncology*. 2011.

[39] J. M. Argilés, S. Busquets, B. Stemmler, and F. J. López-Soriano, "Cachexia and sarcopenia: Mechanisms and potential targets for intervention," *Curr. Opin. Pharmacol.*, vol. 22, pp. 100–106, 2015.

[40] a. Zembroń-Łacny, W. Dziubek, Rogowski, E. Skorupka, and G. Dabrowska, "Sarcopenia: Monitoring, molecular mechanisms, and physical intervention," *Physiol. Res.*, vol. 63, no. 6, pp. 683–691, 2014.

[41] R. Calvani, F. Marini, M. Cesari, M. Tosato, S. D. Anker, S. Von Haehling, R. R. Miller, R. Bernabei, F. Landi, and E. Marzetti, "Biomarkers for physical frailty and sarcopenia: State of the science and future developments," *Journal of Cachexia, Sarcopenia and Muscle*. 2015.

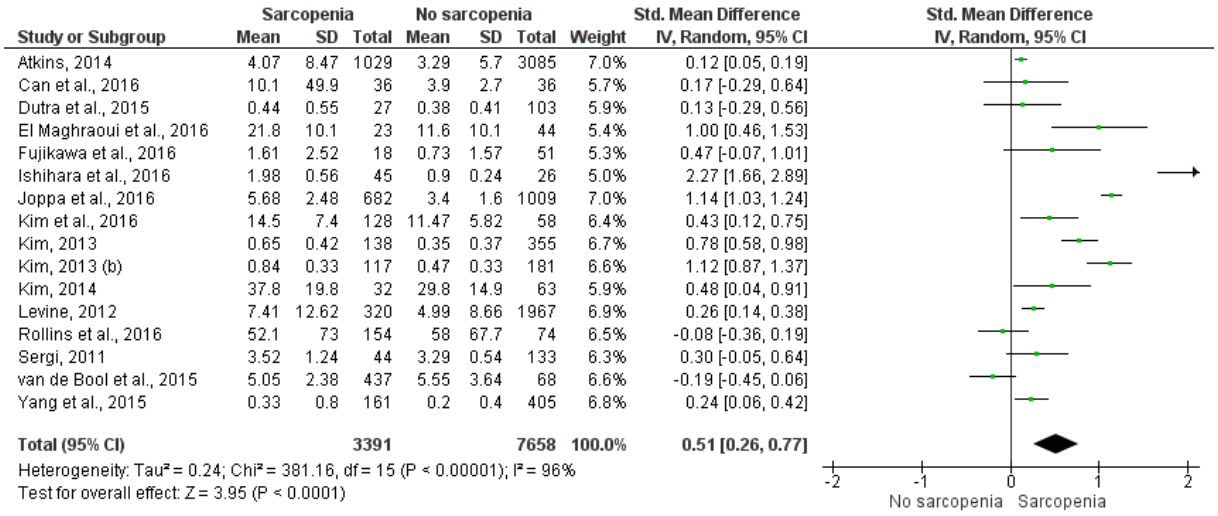
[42] K. J. Berkley, S. S. Zalcman, and V. R. Simon, "Sex and gender differences in pain and inflammation: a rapidly maturing field.," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 291, no. 2, pp. R241–4, Aug. 2006.

[43] I. Rieu, H. Magne, I. Savary-Auzeloux, J. Averous, C. Bos, M. a. Peyron, L. Combaret, and D. Dardevet, "Reduction of low grade inflammation restores blunting of postprandial muscle anabolism and limits sarcopenia in old rats," *J. Physiol.*, vol. 587, no. 22, pp. 5483–5492, 2009.

[44] F. Landi, E. Marzetti, R. Liperoti, M. Pahor, A. Russo, A. M. Martone, G. Colloca, E. Capoluongo, and R. Bernabei, "Nonsteroidal anti-inflammatory drug (NSAID) use and sarcopenia in older people: results from the ilSIRENTE study.," *J. Am. Med. Dir. Assoc.*, vol. 14, no. 8, pp. 626.e9–13, Aug. 2013.

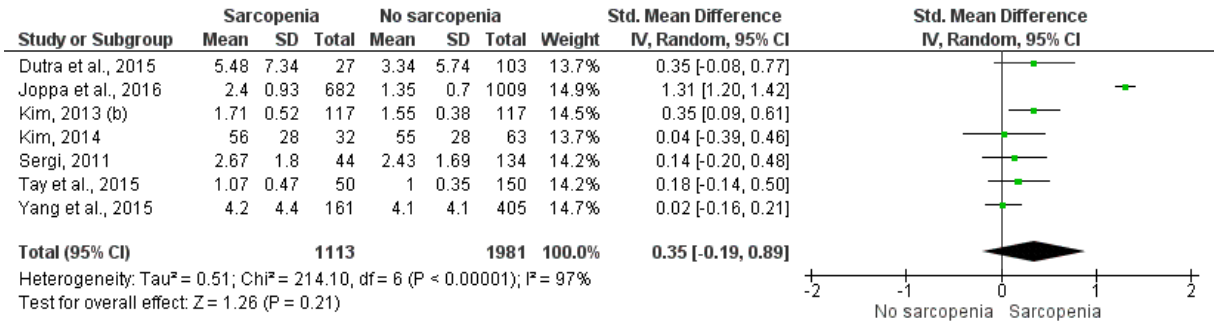
FIGURE LEGEND

Figure 1. Forrest plot of serum high sensitivity C-reactive protein (CRP) in sarcopenic vs. no sarcopenic subjects



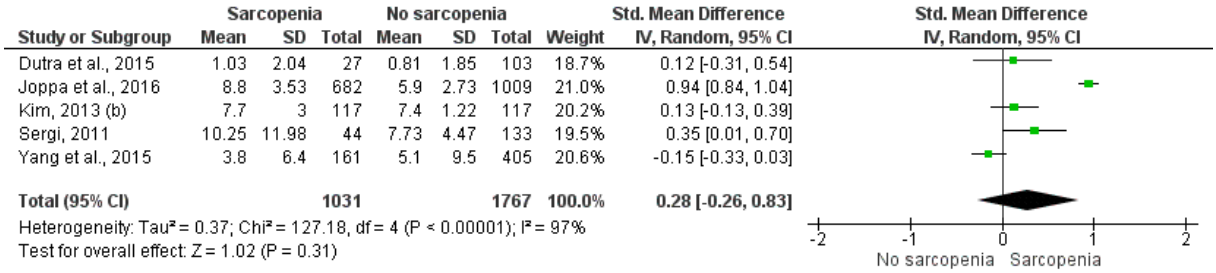
Abbreviations: SD: standard deviation; CI: confidence interval.

Figure 2. Forrest plot of serum interleukin 6 (IL6) in sarcopenic vs. no sarcopenic subjects.



Abbreviations: SD: standard deviation; CI: confidence interval.

Figure 3. Forrest plot of serum tumor necrosis factor alpha (TNF-α) in sarcopenic vs. no sarcopenic subjects.



Abbreviations: SD: standard deviation; CI: confidence interval.